Amendments to the Sequence Listing:

Please replace the pages numbered 1 to 3 of the originally filed Sequence Listing with the attached pages numbered 1 to 7 of the Substitute Sequence Listing submitted concomitantly herewith.

Amendments to the Drawings:

The attached sheet of drawings includes changes to Fig. 1. This sheet, which includes Figs. 1-2, replaces the original sheet including Figs. 1-2. In Figure 1, the word "Drawings" has been deleted.

Attachment: Replacement Sheet
Annotated Sheet Showing Changes

R E M A R K S

Priority Claim Under 35 USC 119

The Examiner is respectfully requested to acknowledge applicant's claim for priority under 35 USC 119 and receipt of the certified copies of the priority documents which were received by the USPTO (see the NOTICE OF ACCEPTANCE OF APPLICATION UNDER 35 U.S.C. 371 AND 37 CFR 1.495 dated October 10, 2006).

In item no. 2 on page 2 of the February 19, 2008 Office Action, the Examiner "noted" that English-language translations of the priority documents have not been provided.

A certified copy of a priority document is defined in MPEP 201.14(b) as follows:

> "The certified copy which must be filed is a copy of the original foreign application with a certification by the patent office of the foreign country in which it was filed. Certified copies ordinarily consist of a copy of the specification and drawings of the application as filed with a certificate of the foreign patent office giving certain Information."

It is respectfully submitted that the certified copies of the priority documents filed in the above-identified application comply with MPEP 201.14(b).

To perfect applicant's claim for priority under 35 USC 119, submitted concomitantly herewith are English-language translations of applicant's two Japanese priority applications (JP 2003-378039 and JP 2004-121080), along with a STATEMENT OF ACCURACY OF TRANSLATION (signed by Dr. Toshiaki YAGUCHI on April 14, 2008) for each Japanese priority application.

Information Disclosure Statements

The February 19, 2008 Office Action enclosed copies of the INFORMATION DISCLOSURE STATEMENTS BY APPLICANT Forms PTO/SB/08A dated May 2, 2006; Form PTO/SB/08B dated June 23, 2006; and Forms PTO/SB/08A and PTO/SB/08B dated August 3, 2006, with the Examiner's initials in the left column next to some of the cited publications.

The Examiner drew lines through the following publications on sheet 1 on the Form PTO/SB/08A dated May 2, 2006 and on the Form PTO/SB/08B dated June 23, 2006 for the following reasons:

Ids Date	Publication	Examiner's Reasons For Not Considering Publication
May 2, 2006	JP 2000-297097	Not in English, not considered
June 23, 2006	**English-language** International Search Report on Patentability mailed May 18, 2006 of PCT/JP2004/016715	Not in English, not considered

The May 22, 2006 Form PTO/SB/08B indicated that an English-language abstract of JP 2000-297097 was enclosed. Page 1 of the May 2, 2006 INFORMATION DISCLOSURE STATEMENT stated the following concerning JP 2000-297097:

> "...JP 2000-297097, which is the published application corresponding to JP 3420984. JP 3420985 is discussed in the specification of the above-identified application."

JP 3420984 is discussed in the paragraph bridging pages 4 and 5 of the present specification.

Clearly the requisite statement of relevancy for JP 2000-297097 was provided by the applicant.

The International Report on Patentability in the June 23, 2006 IDS **was in English** and therefore should have been considered by the Examiner.

The following publications were not initialed by the Examiner on the Form PTO/SB/08B (sheet 3) dated August 2, 2006 and no reasons were provided by the Examiner why such publications were not initialed:

> Björn TEWS et al., "Application of the C4[1]-Alkylated Deoxyribose Primer System (CAPS) in Allele-Specific Real Time PCR for Increased Selectivity in Discrimination of Single Nucleotide Sequence Variants," Biol. Chem., (2003), Vol. 384, pp. 1533-1541.
>
> Makoto KOIZUMI et al., "Improvement of single nucleotide polymorphism genotyping by allele-specific PCR using primers modified with an ENA residue," Analytical Biochemistry, (2005), 340, pp. 287-294.

In view of the above, the Examiner is respectfully requested to return fully initialed copies of the Form PTO/SB/08A dated May 2, 2006, Form PTO/SB/08B dated June 23, 2006 and Form PTO/SB/08B (sheet 3) dated August 3, 2006, with the Examiner's initials in the left column next to each cited publication to indicate that each publication was considered and made of record.

An INFORMATION DISCLOSURE STATEMENT is being filed concomitantly herewith.

Amendment to Page 18 of the Specification

The paragraph bridging pages 17 and 18 of the specification was amended to correct a minor clerical error.

Drawing Objection

Fig. 1 was objected to for the reason set forth in item no. 3 at the bottom of page 2 of the February 19, 2008 Office Action.

A replacement drawing for Fig. 1 is submitted concomitantly herewith. Withdrawal of the drawing objection and approval of the drawings are respectfully requested.

Title

In item no. 4 on page 3 of the February 19, 2008 Office Action, the Examiner stated that the title of the invention was not descriptive and that a new title is required which is indicative of the present claims. The title was amended hereinabove to conform to the title suggested by the Examiner, namely "OLIGONUCLEOTIDES HAVING A 2'-O,4'-C-ETHYLENE NUCLEOTIDE IN THE THIRD POSITION OF THE 3' END."

Trademarked Term

In item no. 5 on page 3 of the February 19, 2008 Office Action, the Examiner objected to the term "Chromolith Performance RP-18e" (see page 65, lines 4 and 13; page 87, lines 10 and last line; and page 88, line 1 of the specification).

The specification was amended hereinabove to define

"CHROMOLITH®" as "a HPLC column containing a single rod of high purity monolithic silica." The undersigned found the above definition on the Internet (see the enclosed copy of MERCK "CHROMOLITH® HPLC COLUMNS").

Sequence Listing

In item no. 6 on pages 3 to 4 of the February 19, 2008 Office Action, it was stated that the application fails to comply with the USPTO Sequence Listing Rules (37 CFR 1.821 to 1.825) because pages 64 to 79, 86 and 88 to 92 contain sequences without SEQ ID NOS. A NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES was attached to the Office Action.

The Examiner was apparently referring to the sequences set forth in the specification as follows: page 64, lines 7 to 8, page 66, lines 5 to 6; page 66, lines 16 to 17; page 67, lines 8 to 9; page 67, line 17; page 68, line 6; page 68, lines 15 to 16; page 69, lines 10 to 11; page 70, lines 6 to 7; page 71, lines 1 to 2; page 71, lines 15 to 16; page 72, lines 9 to 10; page 73, lines 4 to 5; page 73, last two lines; page 74, lines 1 to 15; page 75, lines 5 to 6; page 75, lines 14 to 15; page 76, lines 11 to 12; page 77, lines 3 to 4; page 77, last two lines; page 78, lines 11 to 12; page 79, lines 6

to 7; page 86, lines 12 to 13; page 86, lines 16 to 17; page 88, lines 14 to 16; page 89, lines 5 to 8; page 89, last four lines; page 90, lines 7 to 10; page 90, lines 16 to 18; page 91, lines 6 to 9; page 91, last two lines; and page 92, lines 1 to 2.

Submitted concomitantly herewith are the following:

(1) a copy of said NOTICE;

(2) a Substitute Sequence Listing (computer readable form and paper copy); and

(3) a STATEMENT UNDER 37 CFR 1.821(f)&(g) signed by Dr. Yoshiaki YAGUCHI, dated April 4, 2008.

The specification was amended hereinabove to include SEQ ID NOS. for the sequences on pages 64 to 92 of the specification.

It is respectfully submitted that the application complies with all the requirements of 37 CFR 1.821 to 1.825.

Rejections Under 35 USC 112, Second Paragraph

Claims 1 to 5, 12 to 43 and 52 to 54 were rejected under 35 USC 112, second paragraph, for the reasons set forth in item nos. 8 to 21 on pages 5 to 8 of the February 19, 2008 Office Action.

In item no. 9 on page 5 of the Office Action, the Examiner stated that the terminology in claims 1 and 2 of

"oligonucleotide comprising … (b) … **having** nucleotides complementary to the nucleotide sequence of a reference gene" is indefinite.

Item (b) in claims 1 and 2 were amended to delete the term "having."

Following the Examiner's suggestion, an item (c) was added to claims 1 and 2.

Item (c) in clams 1 and 2 as amended hereinabove reads as follows: "nucleotides complementary to a nucleotide sequence of the target gene."

The meaning of the term "complementary nucleotide" is defined on page 29, lines 1 to 4 in the present specification as "a nucleotide with a base portion complementary to that of another nucleotide." The nucleotide base pairs complementary to each other are adenine and thymine; guanine and cytosine; or adenine and uracil.

It is respectfully submitted that one of ordinary skill in the art would know the meaning of the phrase "nucleotides complementary to a nucleotide sequence of the target gene" as recited in applicant's claims 1 and 2.

In item nos. 10 and 11 on pages 5 to 6 of the February 19, 2008 Office Action, the Examiner took the position that in claims 3, 4 and 12 to 17, the terminology of "the nucleotides complementary to the nucleotides of the target gene" was

indefinite.

Claims 3, 4 and 12 to 17 were amended hereinabove to recite "a region of the nucleotides complementary to a region of the target gene."

In item no. 13 at the middle of page 6 of the February 19, 2008 Office Action, the position was taken by the Examiner that the terminology of "a sequence of interest" in claims 12 to 17 were indefinite.

On page 38, last paragraph in the present specification, the following is disclosed: "the sequence of interest in a gene used as a target in PCR." The term "a sequence of interest" recited in applicant's present claims 12 to 17 is the same as this phrase.

In item nos. 14 to 16 on pages 6 to 7 of the February 19, 2008 Office Action, the Examiner took the position that the terminologies of "the reference nucleotide of a target gene" (claims 14 and 15), "the nucleotide of a reference gene" (claims 15 to 17) and "the mutant nucleotide of a target gene" lack antecedent basis.

Claims 14, 15 and 17 were amended hereinabove to recite "**a** reference nucleotide of a target gene"; "**a** nucleotide of a reference gene," and "**a** mutant nucleotide of a target gene."

In item nos. 18 to 21 on pages 7 to 8 of the Office Action, the terminologies of "disease-associated gene" (see

claims 23, 29, 35 and 41), "causative gene" (see claims 24, 30, 36 and 42) and "a dopamine D3," "an angiotensin precursor" and "a blood coagulation factor VII" (see claims 25, 31, 37 and 43) were alleged to be indefinite.

To clarify the meaning of these phrases, submitted herewith is a copy of Shastry, "SNPs in Disease Gene Mapping, Medicinal Drug Development and Evolution," Journal of Human Genetics, (2007), Vol. 52, pp 871-880.

The term "disease-associated gene" is a gene whose association with diseases is known and these genes are well-known to a person having ordinary skill in the art. A partial list of diseases associated with single nucleotide polymorphisms is disclosed on page 872, Table 1 of Shastry.

The term "causative gene" means a gene which causes a disease associated with its polymorphism, such as single nucleotide polymorphism. This would be clear to a person having ordinary skill in the art. Examples of these genes as disclosed on page 3, second paragraph of the present specification are as follows: HLA, TCRα, APOE4, a dopamine D3 receptor, tryptophan hydroxylase, an angiotensin precursor, blood coagulation factor VII and leptin.

A drug metabolizing gene is a gene which encodes drug metabolizing enzymes. On page 874, Table 2 in Shastry, a partial list of such genes is set forth. Examples of these

genes as disclosed on page 32, second paragraph, in the present specification are as follows: cytochrome P4501A2, cytochrome P4502A6, cytochrome P4502C9, cytochrome P4502C19, cytochrome P4502D6 and cytochrome P4502E1.

It is respectfully submitted that for a person having ordinary skill in the art, the meaning of the term "drug metabolizing gene" would be clear.

In view of the above, withdrawal of the 35 USC 112 rejection is respectfully requested.

Claims 1 to 5, 23, 29 and 41 were rejected under 35 USC 103 as being unpatentable over Latorra et al., Human Mutations, (2003), 22, 79-85 and Koizumi et al., Nucleic Acids Research, (2003), 13, No. 12, 3267-3273 for the reasons set forth in item no. 23 on pages 8 to 10 of the February 19, 2008 Office Action.

It was admitted at the top of page 10 of the February 19, 2008 Office Action that Latorra et al. do not specifically teach a 2'-O,4'-C-ethylene nucleotide (ENA) unit.

It was also admitted at the middle of page 10 of the February 19, 2008 Office Action that Koizumi et al. do not specifically teach an oligonucleotide comprising ENA units at the third position from the 3' end.

The following is stated in the last three lines on page 8 of the February 19, 2008 Office Action regarding Latorra et

al.:

> "...by teaching that the LNA nucleotide can be placed in any of the four positions, including the third position, from the 3' end of an oligonucleotide as given in Table 1."

In the legend of Table 1 on page 8 of Latorra et al., the following is stated:

> "A total of 16 forward DNA and 3' LNA primers were designed or each of three pUC19 targets, and included match and the three other possible mismatch combinations at the last four positions of each 3' end."

Although the above sentence discussed the possibility of placing a nucleotide in any of the four positions from the 3' end, there is no description or suggestion for placing a LNA nucleotide in any of the four positions from the 3' end. In Latorra et al., a LNA nucleotide is fixed at the 3' end.

Accordingly, Latorra et al. do not teach or suggest an oligonucleotide comprising a 2'-O,4'-C-methylene nucleotide (ENA) unit **which is the third nucleotide form the 3'-end of the oligonucleotide**, wherein the nucleotide at the 3'-end is defined as the first nucleotide, and the other nucleotides are natural nucleotides, as recited in applicant's present claims.

In the last two lines on page 9 of the February 19, 2008 Office Action, the position was taken by the Examiner that Latorra et al. teach an oligonucleotide comprising "(d) a nucleotide which is the third nucleotide from the 3'-end

position of each oligonucleotide is a 2'-O,4'-C-methylene nucleotide (LNA) unit." As discussed hereinabove, a LNA nucleotide is fixed at the 3'-end in Latorra et al., so such statement regarding the disclosure in Latorra et al. is incorrect.

The following was stated in the first sentence of the fourth paragraph on page 10 of the February 19, 2008 Office Action:

> "Latorra et al. teach oligonucleotides comprising LNA units at the third position from the 3' of an oligonucleotide."

As explained above, this allegation is incorrect.

Claims 12 to 19 and 52 to 54 were rejected under 35 USC 103 as being unpatentable over the aforesaid Latorra et al. publication, the aforesaid Koizumi et al. publication and Weston et al. (USP 6,391,593) for the reasons stated in item no. 24 on pages 11 to 17 of the February 19, 2008 Office Action.

It was admitted at the top of page 16 of the February 19, 2008 Office Action that Latorra et al. do not specifically teach a 2'-O,4'-C-ethylene nucleotide (ENA) unit and do not specifically teach a kit.

It was admitted at the middle of page 16 of the February 19, 2008 Office Action that Koizumi et al. do not specifically

teach a kit.

In item no. 24 on page 16 of the February 19, 2008 Office Action, the following position was taken:

> "Weston et al. teach kits comprising oligonucleotides with LNA units, DNA polymerases and PCR buffers (see column 7, lines 41 to 51, and see claims 20 and 21)."

Weston et al. do not specify the position and number of LNA units in their probes. In contrast thereto, applicant's claims specify the position (the third position) and number (one) of an ENA unit (the third nucleotide from the 3'-end thereof is a 2'-,4'-ethylene nucleotide (ENA) unit, wherein the nucleotide at the 3'-end is defined as the first nucleotide).

In addition, Weston et al. disclose a kit which comprises a following pair of probes:

(a) first probe: comprising a portion complementary to the sequence of interest and capable of hybridizing thereto, and a portion non-complementary to the sequence of interest;

(b) second probe: comprising a portion complementary to the sequence of interest and capable of hybridizing thereto, and a portion non-complementary to the sequence of interest, but complementary to that portion of the first probe

which is non-complementary to the sequence of interest.

The structure of said pair of probes in Weston et al. is completely different from applicant's claims. It is therefore respectfully submitted that Weston et al. do not teach or suggest applicant's claimed kits.

Claims 20 to 22, 24 to 28, 30 to 40 and 42 to 43 were rejected under 35 USC 103 as being unpatentable over the aforesaid Latorra et al. publication, the aforesaid Koizumi et al. publication and Stanton et al. (US 2001/0034023) for the reasons indicated in item no. 28 on pages 17 to 18 of the February 19, 2008 Office Action.

It was admitted on page 17 of the February 19, 2008 Office Action that Latorra et al. and Koizumi et al. do not teach the features of applicant's claims 20 to 22, 24 to 28, 30 to 40 and 42 to 43.

In item no. 25 on page 17 of the February 19, 2008 Office Action, the following position was taken:

> "Staton et al. teach oligonucleotide/primers for detecting drug metabolizing genes."

Stanton et al. do not teach or suggest an oligonucleotide as recited in applicant's claims (the third nucleotide from the 3'-end thereof is a 2'-O,4'-ethylene nucleotide (ENA) unit, wherein the nucleotide at the 3'-end is defined as the

first nucleotide) for detecting drug metabolizing genes.

It is respectfully submitted that all the obviousness rejections are based on a misinterpretation of Latorra et al.

Latorra et al. teach only nucleotides whose LNA nucleotide is fixed at the 3' end. In contrast thereto, applicant's claims are directed to nucleotides whose ENA nucleotide unit is the third nucleotide from the 3'-end. The nucleotide recited in applicant's claims is thus completely different from the nucleotides disclosed in Latorra et al.

It is therefore respectfully submitted that one of ordinary skill in the art would not arrive at applicant's present claims in view of the disclosures of the references.

Withdrawal of each of the obviousness rejections is thus respectfully requested.

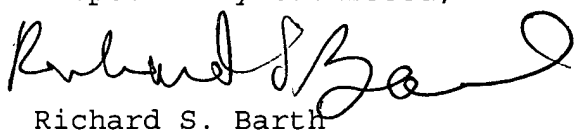
Rejoinder

If the claims of Group I are allowed, rejoinder and allowance of the claims of Group II are respectfully requested (see item no. 3 on pages 4 to 5 of the November 15, 2007 Office Action).

Reconsideration is requested. Allowance is solicited.

If the Examiner has any comments, questions, objections or recommendations, the Examiner is invited to telephone the undersigned at the telephone number given below for prompt action.

Respectfully submitted,



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Encs.: (1) English-language translation of JP 2003-378039 and JP 2004-121080, each with a STATEMENT OF ACCURACY OF TRANSLATION of Dr. Toshiaki YAGUCHI dated April 4, 2008
(2) copy of NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES
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(5) copy of MERCK "CHROMOLITH® HPLC COLUMNS
(6) copy of J. Hum. Genet., (2007), 52: 871-880
(7) INFORMATION DISCLOSURE STATEMENT

~~Drawings~~

Figure 1

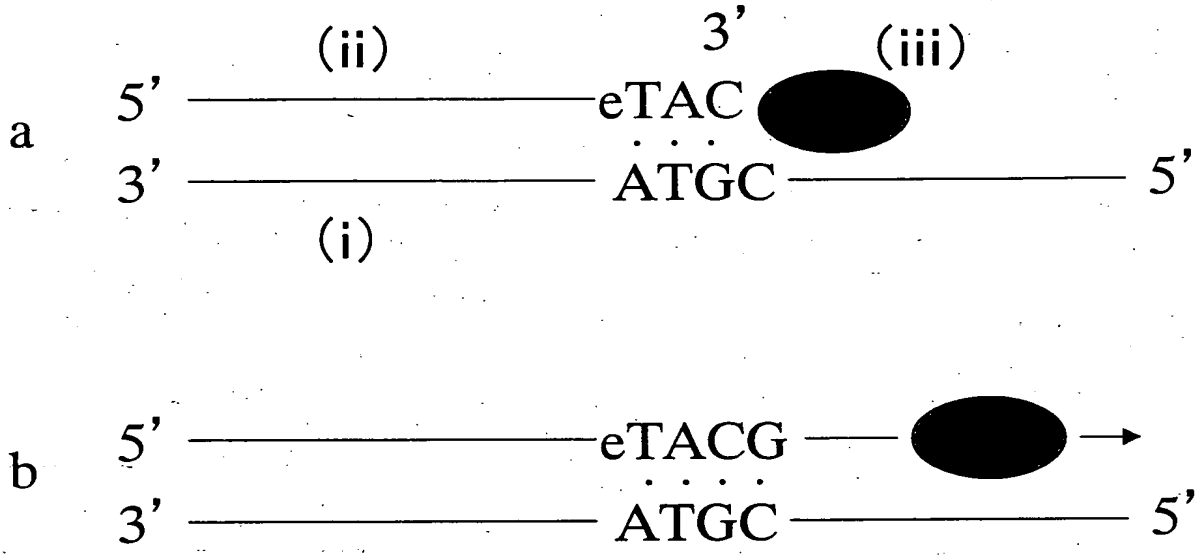

Figure 2